

Statistical Analysis for Hyper-radiosensitivity/Radioresistance Physical Model of Irradiated Cell

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Abstract

This study investigates the hyper-radiosensitivity (HRS) and induced radioresistance (IRR) effects in cells exposed to low-dose radiation, focusing on identifying critical dose thresholds and exploring underlying molecular mechanisms. By analyzing cell survival data using a normal distribution-based mathematical model, we determined two key dose thresholds: D_0 , where repair mechanisms are activated, and D_1 , where repair and damage rates equilibrate. Our findings reveal that ATM (ataxia-telangiectasia mutated) and p53 proteins play central roles in modulating these thresholds, with wild-type p53 cells demonstrating faster repair initiation and mutant p53 cells exhibiting broader response curves. The results show that cellular outcomes depend on both genetic background and radiation dose, with potential implications for optimizing radiotherapy protocols and developing radioprotective strategies. This work provides a quantitative framework for understanding HRS and IRR phenomena and contributes to advancing personalized approaches in radiation medicine.

Keywords Hyper-radiosensitivity · Induced radioresistance · Low-dose radiation · ATM protein · P53 protein · Cell repair mechanisms

Introduction

The application of nuclear technology has been instrumental across industry, agriculture and scientific research, notably in areas such as industrial irradiation and diagnostic imaging. In most cases, people are primarily exposed to low-dose radiation, while high-dose radiation exposure is extremely rare.

Early theoretical models generally described radiation-induced damage as following a linear or exponential dose-effect relationship (illustrated in the high-dose range of Fig. 1). However, due to limited experimental conditions, including imprecise techniques for cell dilution, counting, and inoculation, significant random errors were introduced. As a result, cell survival at radiation dose

below 1 Gy cannot be accurately observed. Therefore, the cell survival fraction in the sub-1 Gy range was mainly extrapolated from the radiation biological effect data of Linear Quadratic (LQ) Models[1]. With advances in experimental techniques such as flow cytometry, microscopic localization , both the measurement accuracy and statistical reliability of cell survival fractions have significantly improved, facilitating more precise studies of cell survival under low-dose radiation conditions, as shown in the low-dose range of Fig. 1.

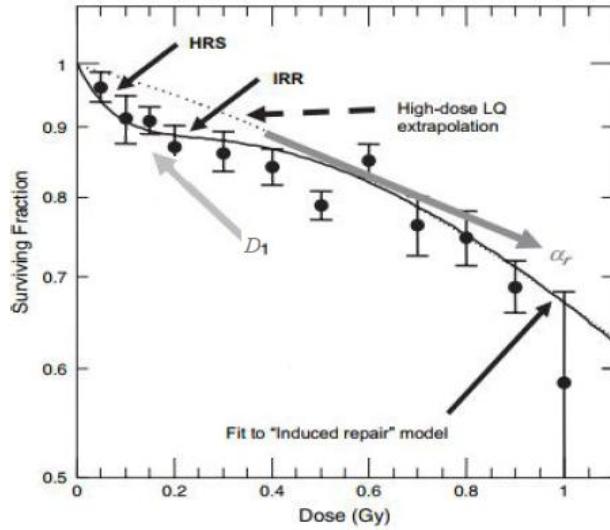


Fig. 1 Cell survival fraction curve[2]

In 1963, Eriksson G conducted experiments on maize exposed to γ rays, finding that the mutation rate and mortality rate of maize pollen grains under low dose (< 0.5 Gy) radiation increased significantly, compared with those under high-dose exposure. This discovery led him to propose the concept of low-dose hyper-radiosensitivity (HRS) response.[3] It has been suggested that HRS responses are associated with radiation doses below 0.3 Gy, while doses within the 0.3-0.6 Gy range induce increased radioresistance (IRR).[4, 5] Jin later observed that high liner energy transfer (LET) radiation from ^{12}C ions also triggers HRS/IRR responses in the dose range between 0 and 2.5 Gy, with HRS appearing at doses below 0.75 Gy(shown in Fig. 2[6]). Additionally, our study identified the HRS phenomenon in *C. elegans*, but occurring at a higher dose threshold below 20 Gy.[7] The HRS/IRR phenomenon has proven to be of great significance in the context of low-dose radiation protection for occupational staff and for normal tissue protection during radiotherapy.[8]

Human hepatoma cells (SMMC-7721) were irradiated with ^{60}Co γ rays and 50 MeV/ u ^{12}C ions, respectively. The HRS/IRR reaction curve observed in these cells was found to fit the model, as expressed in formula (1)[6]:

$$F_{-1}(D) = \exp(-\alpha D - \beta D^2) \quad (1)$$

where $F_{-1}(D)$ denotes the survival fraction of hepatocellular carcinoma (HCC) cells; D is the absorbed dose in Gy; αD represents the direct cell death effect caused by single dose of

radiation, while β / D corresponds to the cumulative lethal effects of radiation damage. The parameter α is defined as follows:

$$\alpha = \alpha_{res} - [1 + (\alpha_{sen} / \alpha_{res}) - 1]e \times p \quad (2)$$

where α_{res} is the slope derived from the LQ model; α_{sen} is the slope derived from IR model; D_1 represents the absorbed dose at the inflection point of the curve, Gy. Experimental results indicate that the dose threshold for inducing HRS by ^{60}Co γ rays and ^{12}C ions is 0.33 Gy and 0.28 Gy, respectively.

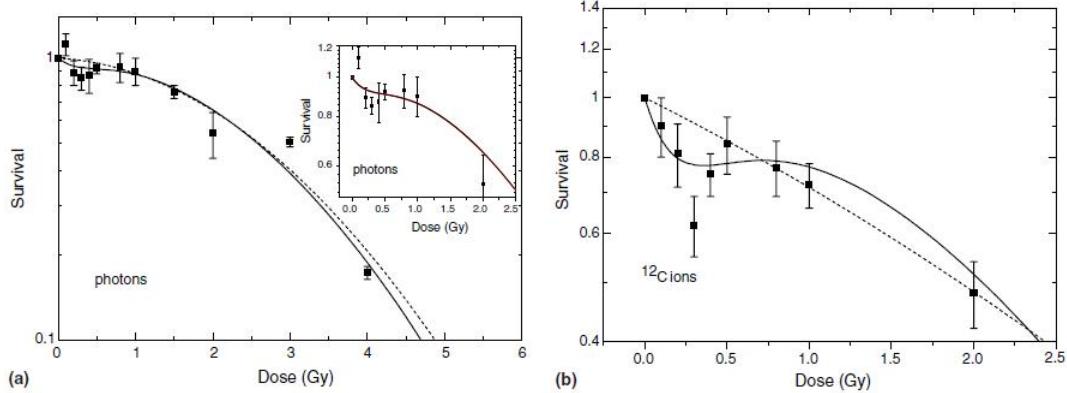


Fig. 2 Survival Fraction for individual samples obtained with the cell sorter, (a)photon irradiation and (b)50 MeV/u carbon irradiation

The Normal distribution is a key probability distribution widely used in mathematics, physics, engineering, and various statistical applications. HRS and IRR phenomena are generally considered as two distinct states: “repair uninitiated” and “repair initiated”, representing different phases within the probability distribution of radiation-induced damage and repair processes. This paper proposes that the low-dose HRS/IRR phenomenon follows a normal distribution and seeks to establish a consistent morphological mathematical model for HRS/IRR curves by fitting extensive HRS/IRR data to this model.

Hypothesis and Analysis

The prevailing theory of the HRS phenomenon suggests a “cellular radar” mechanism that plays a crucial role in the repair of DNA double-strand breaks (DSBs)[9]. When radiation-induced DNA damage is below a certain threshold, this “cellular radar” does not detect the radiation damage, leaving the immune system inactive in the low-dose range. As a result, radiation appears more severe than estimated by LQ model, a condition termed HRS. As the dose increases, the “cellular radar” begins to detect damage, activating the immune response and increasing the repair rate, leading to IRR characteristics in the survival curve.

In order to analyze the HRS/IRR data in the research work, we first proposed three hypotheses as follow:

- 1) In the absence of irradiation, cells remain in a stable, homeostatic state, characterized by the stability of DNA molecules, as well as the stability of biological signal molecules and associated proteins within each cell.
- 2) When cells are exposed to ionizing radiation, the damage extends beyond the traditional radiation target (DNA) damage, also affecting essential biological signaling molecules. This broad damage results in structural changes and functional decline across multiple molecular types.
- 3) Following exposure to ionizing radiation, there are two procedures of damage and repair in cells. When the cell damage rate exceeds the self-repair rate, the survival rate declines, and vice versa. When both are equal, the survival rate remains stable.

Based on the above hypothesis, we speculate that the survival rate of cells in low-dose range follows a normal distribution, denoted as $F_2(D)$, and referred to as the Damage-Repair Response (DRR). Specifically, the response variable follows a probability distribution characterized by a low-dose parameter D_0 and a scale parameter σ , with the probability distribution function defined as:

$$F_2(D) = \frac{A}{\sqrt{2\pi}} e^{-\frac{(D - D_0)^2}{2\sigma^2}} \quad (3)$$

where D is the absorbed dose, Gy; D_0 is the initiation point of DNA DSB repair, Gy; σ characterizes the acute repair dispersion parameter of cells; A is the normalized coefficient for the normal distribution.

When the dose is below D_0 , the “cellular radar” does not detect radiation damage, making the damage rate the dominant factor. Based on the above first and second hypothesis, radiation-induced damage of DNA molecules, biological signaling molecules, and associated proteins disrupts the original homeostatic state, resulting in the appearance of HRS. As the dose increases, the “cellular radar” detects the radiation damage and activates the repair mechanism at D_0 above.

In line with previous research suggesting that radiation damage follows an exponential dose-response relationship, we speculate that cell survival fraction can be fitted by the sum of a normal function and an LQ function. Namely, the formula is:

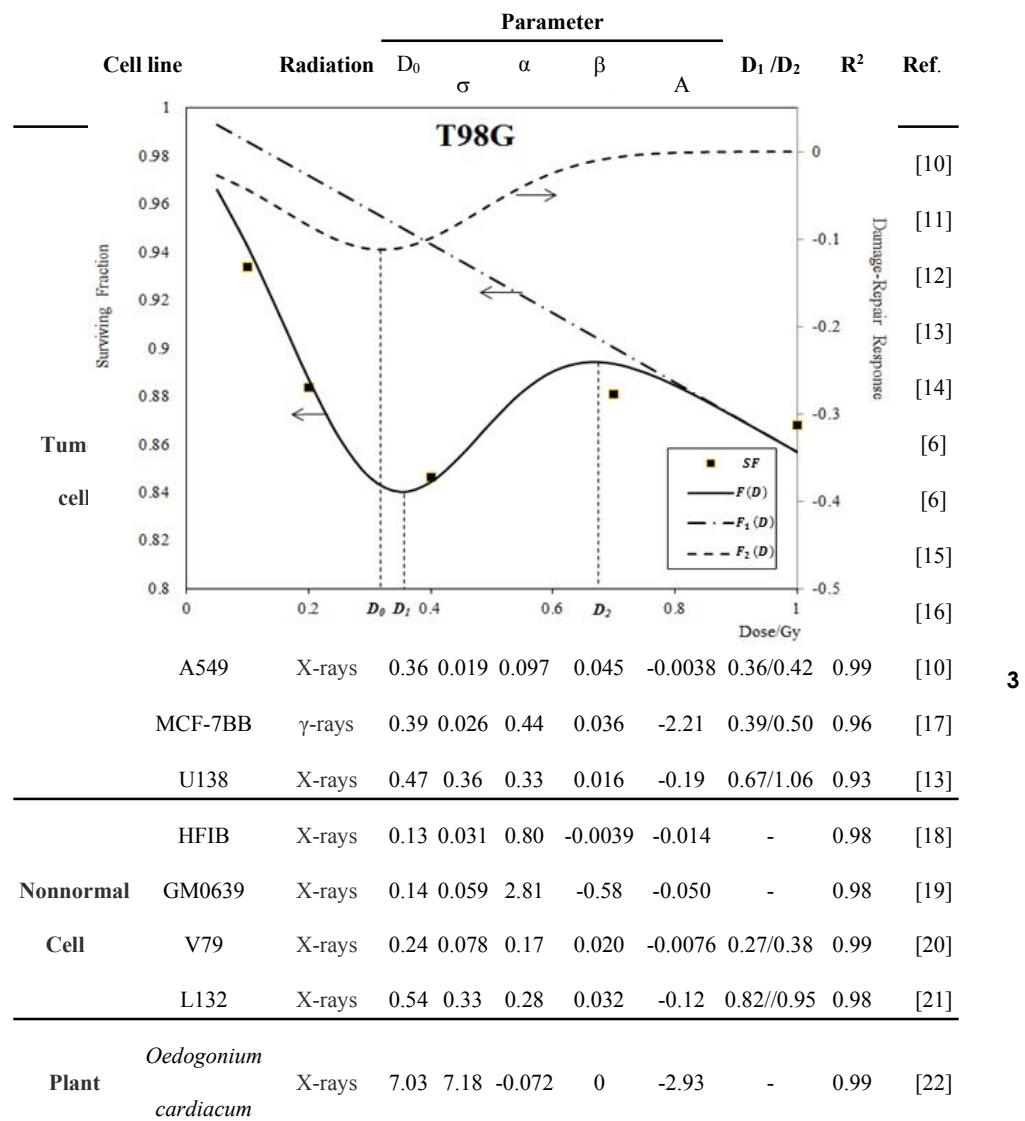
$$F(D) = F_1(D) + F_2(D) = \frac{A}{\sigma \sqrt{2\pi}} e^{-\frac{(D - D_0)^2}{2\sigma^2}} +$$

$$e \times p \quad (-\alpha D - \beta D^2) \quad (4)$$

where $F(D)$ represents cell survival fraction.

We obtained some experimental results on low-dose HRS of tumor cells and normal cells through the consult literature material. Curve fitting was performed using MATLAB's least square method. After the fitting results, relevant parameters (D_0 , σ , α , β and A) were listed in Table 1, and the correlation coefficients R^2 for all curve fitting were greater than 0.9. To identify the inflection points between the HRS and IRR regions, as well as from IRR region to high dose, which are D_1/D_2 value, the derivative of formula (4) was taken. When $d(F(D)) / dD = 0$, the D_1/D_2 values were obtained, as summarized in Table 1.

Table 1 Values of the parameter of the HRS/IRR model used to fit the survival fraction



Typical low dose HRS curve

To elucidate the characteristics of HRS/IRR, we selected T98G cells as a representative example. According to Formula (4), the survival fraction is modeled as a combination of a normal distribution and an exponential function. The components of $F_1(D)$, $F_2(D)$, $F(D)$ along with experimental results from literature, are presented in Fig. 3.

As shown in Fig. 3, when T98G cells were irradiated with a dose less than D_0 , the “cellular radar” does not detect radiation damage, resulting in a damage-dominant response and a decrease in survival fraction as dose increases. When the dose reaches D_0 , the “cellular radar” detects radiation damage and initiates a cellular repair mechanism. It can be seen from Table 1 that $D_0 = 0.32$ Gy represents the minimum value of the $F_2(D)$ function in Fig. 3. For dose greater than D_0 , based on the above third hypothesis, the repair rate increases, though it remains lower than the damage rate, causing $F(D)$ to continue decreasing. When the dose reaches D_1 , the repair rate equals the damage rate, representing a homeostatic point and the transition from HRS to IRR, as shown in Table 1 with $D_1 = 0.35$ Gy, the minimum value of $F(D)$ function in Fig. 3. Thus, when $D < D_1$, T98G cells survival fraction exhibits HRS characteristics.

For doses above D_1 , as shown in Fig. 3, the $F(D)$ value is increasing, due to the repair rate surpasses the damage rate, even though damage rate continues to rise slowly as shown in $F_1(D)$. When the dose reaches D_2 , the repair and damage rates are again balanced, as shown in $F(D)$. When $D_1 < D < D_2$, $F(D)$ curve shows the characteristic of IRR. According to Table 1, $D_2=0.67$ Gy is the maximum value of $F(D)$ in Fig. 3, marking the inflection point from IRR to high-dose behavior. For doses exceeding D_2 , the damage rate significantly exceeds the repair rate, with $F_1(D)$ becoming dominant and repair rate in $F_2(D)$ being negligible.

To further investigate the changes of HRS/IRR and the corresponding cellular regulating mechanisms, we analyzed key biological factors associated with DNA damage repair and morphological characteristics, namely P53 type and ATM levels. The activation level of ATM after irradiation is positively correlated with the inflection point of normal distribution, while type of P53 (wild-type or mutant) is related to σ values. The relationships among cell damage repair parameters, morphological characteristics, and normal distribution features are discussed in this paper.

Discussion

In this study, we propose that formula (4) is applicable to analysis of all cell survival fractions and exhibits generalizability across various cell types. The implications of formula (4) are outlined as follows:

- 1) If a survival curve does not display HRS/IRR phenomena in the low-dose region, A is set to zero, rendering the survival curve exponential in form. This indicates the absence of HRS/IRR characteristics in such cells.
- 2) When HRS/IRR phenomena are present but relatively weak in the low-dose region, A takes a small value, and D_1/D_2 values are failed to obtain in formula (4). This scenario applies to cells like DU145 prostate cancer cells, HeLa cervical cancer cells, Be11 melanoma cells and HGL21 glioma cells, which do not exhibit solutions for D_1/D_2 in Table 1, indicating minimal HRS/IRR features.³⁾ For cells with pronounced HRS/IRR phenomena in the low-dose region, A value is large, and D_1/D_2 value are definable. Cells such as HT29 colorectal cancer cells in Table 1 display clear HRS and IRR dose regions.

D_0 and D_1 correlate with differentiation of cell line

Cell differentiation refers to the process by which unspecialized cells develop specialized functions and is categorized into poorly differentiated, moderately differentiated, and well-differentiated types. It is generally accepted that lower differentiation of tumor cells correlates with faster tumor growth and greater sensitivity to radiation damage. To assess the cell differentiation correlation with D_0 and D_1 , the differentiation for tumor cells in Table 1 were investigated, with results shown in Table 2. As seen in Table 2, poorly differentiated tumor cells have relatively smaller D_0 values compared to moderately or well-differentiated tumor cells, indicating a higher sensitivity to radiation damage. Additionally, some poorly differentiated tumor cells lack D_1 values, implying that they do not meet the condition of $d(F(D))/dD = 0$, where the repair rate remains consistently lower than the damage rate. This suggests that the repair rate is insufficient although repair mechanisms may initiate, so causing cell survival to be primarily governed by the damage rate.

Contrary to this trend, the correlation between cell differentiation and sensitivity to radiation damage may be restricted by other factors. For instance, as observed in Table 2, although T98G, glioma cells, though poorly differentiated, display high D_0 and D_1 values. This anomaly may be attributed to

the presence of stem-like cells within these tumors, which possess self-renewal capability and exhibit resistance to radiotherapy [23].

Table 2 Correlation differentiation of tumor cells with D_0 and D_I

Cell line	Differentiation	D_0	D_I
DU145	poorly	0.18	-
HeLa	poorly	0.19	-
Be11	poorly	0.22	-
HT29	well	0.30	0.46
SMMC-7721 (12C ions)	medium	0.30	0.31
T98G	poorly	0.32	0.35
A549	medium	0.36	0.36
MCF-7BB	medium	0.39	0.39

The correlation between P53 gene and σ

The p53 pathway is a complex cellular stress response network with multiple inputs and downstream effects, playing a critical role as a tumor suppressor. Following exposure to ionizing radiation, an ATM-dependent DNA damage response cascade was mediated by the p53 protein[24], as shown in Fig. 4. When DNA damage occurs, ATM phosphorylates p53 at Ser-15 and Chk2 at Thr-68, while Chk2 further phosphorylates p53 at Ser-20 to regulate cell cycle arrest and apoptosis. The proper functioning of p53 is therefore essential for DNA damage repair, apoptosis and radiation-induced cell cycle arrest.

However, missense mutations in the TP53 gene produce mutant p53 proteins ,which been confirmed to increase radiation resistance over the wild-type counterpart[25, 26]. Inappropriate cellular survival after cellular stresses such as irradiation, and inappropriate replication of damaged DNA were caused by mutant p53, thus may finally contribute cell to malignant transformation.

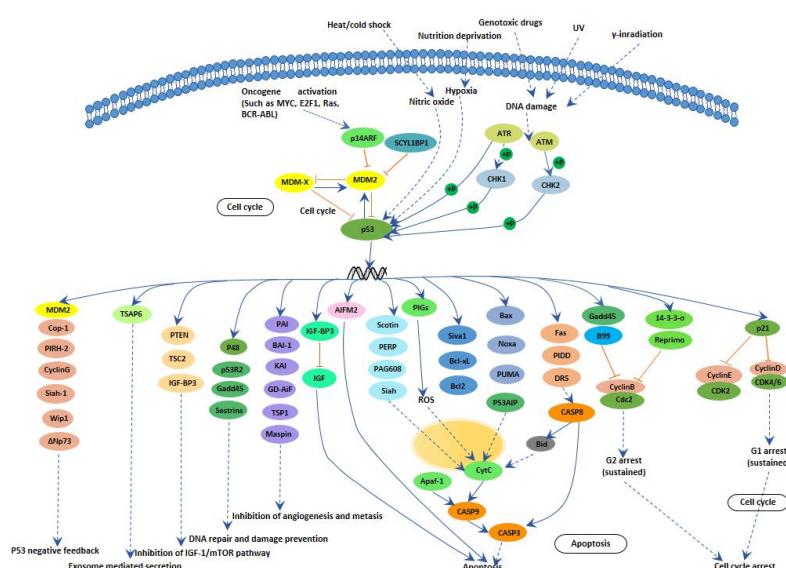


Fig. 4 Cellular Stresses Pathway

Under normal conditions, p53 protein is present at low levels, with slight increases upon perturbations. The response to DNA damage, such as from ionizing radiation, was affected by the changes in p53 levels over time. Cells repair DNA damage and re-enter the cell cycle if wild-type or functioning p53 protein levels pulses following irradiation[27]. As a decision-making transcription factor, p53 selectively activates genes as part of specific gene expression programs following DNA damage to determine cellular fate[25]. Loss of p53 function due to TP53 mutations has recently been shown to increase the resistance to DNA-damaging agents in human tumor cell lines[26].

Mutations in p53, including the six most commonly mutated residues, are mostly loss-of-function mutations, where mutant p53 proteins fail to activate the critical target genes of wild-type p53 necessary for maintaining homeostasis. We hypothesize that the wild/mutant of p53 gene correlates with the σ parameter as shown in Table 3.

Table 3 Comparison of tumor cells P53 type and σ

Cell line	Radiation	σ	Type
DU145	X-rays	0.13	mutant
HT29	X-rays	0.21	mutant
T98G	X-rays	0.16	mutant
RT11	X-rays	0.19	mutant
U138	X-rays	0.36	mutant
HeLa	X-rays	0.093	wild
Be11	X-rays	0.30	wild
SMMC-77 21	^{12}C ions	0.085	wild
SMMC-77 21	X-rays	0.10	wild
A549	X-rays	0.019	wild
MCF-7BB	γ -rays	0.026	wild

As shown in the Table 3, the σ value of wild-type cells are generally smaller than those of mutant cells, indicating a narrower normal distribution curve around D_0 . We infer that wild-type cells are more sensitive to radiation damage, and the repairing response is initiated acutely. In contrast, mutant cells exhibit a more chronic response to radiation damage, characterized by a wider normal distribution. One exception in Table 3 is the Be11 melanoma cell line, possibly due to unique biological characteristics. For example, wild-type melanoma cells do not show radiosensitivity, consistent with clinical radiotherapy resistance, likely related to their poorly differentiated cell type[28].

HRS “cellular radar”: ATM protein

ATM kinases regulate a variety of proteins involved in cell cycle checkpoint, DNA repair and apoptosis. Following ionizing radiation, the ATM kinase, a key regulator of cellular responses to DNA damage, was reported to be activated/phosphorylated[29]. As a critical responder to DNA damage, ATM rapidly initiates responses that control cell cycle progression and other processes. Consequently, we propose that the ATM kinase act as a “cellular radar” for radiation damage as described above, with its kinase activity/phosphorylation levels correlating positively with the DNA damage response events[30].

Ionizing radiation increases the occurrence of DSBs or single-strand breaks (SSBs). The Mre11–Rad50–NBS1(MRN) complex, a “signal modifier”, performs initial resection of broken DNA ends to create structures suitable for repair and recruit signal transducers. Meanwhile, the functional MRN complex activate ATM and its downstream pathways promptly. ATM autophosphorylation converts inactive ATM into a potent protein kinase and makes a fraction of the nuclear content of ATM adheres to the DSB sites^[31] The ATM protein levels peak within 2 hours of exposure to ionizing radiation, with induction beginning within 5 minutes, indication a rapid mechanism. ATM has been demonstrated to act upstream of p53 in an ionizing radiation-induced signal transduction pathway, phosphorylating p53 at serine 15, thereby activating cell cycle checkpoints across G1, S, and G2 phases (see Fig. 5)[32]. In this way, ATM establishes an unanticipated role in the signaling of DNA damage, contributing to genetic stability and preventing malignant transformation.

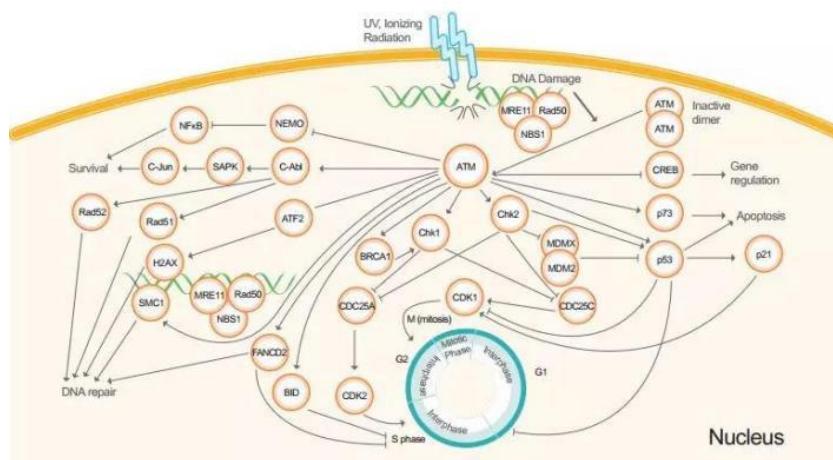


Fig. 5 DNA damage process after radiation

Here, we investigated on ATM protein levels in various cell types and tissues after ionizing radiation, as shown in Fig. 6. In C3ABR cell line, a lymphoblastoid cell line immortalized by Epstein-Barr virus from a healthy female, ATM protein levels fluctuated, a phenomenon not observed previously. Using ImageJ, a Java-based public image processing software developed by the National Institutes of Health, we quantified the concentration of protein in SDS-PAGE gel bands and found interesting phenomena. At a dose of 0.1 Gy, ATM content slightly decreased to 0.86 times its resting level, contradicting the theory that irradiation generally increases ATM levels. Based on the second hypothesis of this study, a plausible explanation is that radiation damage would not only increase the damage rate of DNA, but

also increase the damage rate of ATM and other molecules, resulting in reduced ATM levels. Radman formerly suggested that proteome protection against oxidative damage determines survival fraction after ionizing irradiation was the reason of protein damage determining radiation resistance[33]. Consequently, increased cellular damage rates correspond to the stage of cell survival curve, below D_I . For doses above 0.1 Gy, the expression of ATM rises, enhancing the cell repair rate and correlating with the stage in cell survival curve beyond D_I . Subsequently, ATM expression decreases again, likely due to both direct ATM damage from radiation and MRN complex damage. These findings support the theoretical model of HRS/IRR, illustrating consistent trends between the survival fraction curves and ATM levels.

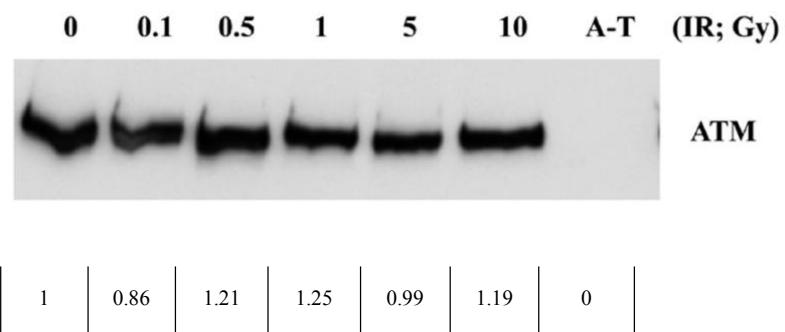


Fig. 6 ATM protein expression in lymphocytes after ionizing radiation (IR)[34]

Conclusion

In this paper, we identified the D_I value derived from formula (4) as the inflection point at which the cell repair rate surpasses the damage rate. Based on our analysis and literature review, we conclude the following:

Below the D_0 threshold, only damage rate exists which shows that the survival rate decreases with increasing dose, as the "cellular radar" ATM molecule fails to detect radiation damage.

When the dose reaches D_0 , ATM has detects radiation damage, giving a trigger signal to activate the cell repair mechanism. In Fig. 3, this threshold is estimated at 0.32 Gy. For dose above 0.32 Gy, cell repair in response to radiation is triggered. In the dose range between 0.32 Gy and 0.35 Gy, the DNA repair rate remains lower than the damage rate due to simultaneous damage to both DNA and protein molecules. Consequently, the cell survival curve exhibits HRS characteristics at doses below 0.35 Gy.

At D_1 , cell repair rate equals the damage rate, correlated with increased level of activated ATM. The D_1 value varies by radiation type. For example, for Hela cells, the D_1 value are 0.28 Gy for ^{60}Co beams, 0.25 Gy for 6 MV X-rays, and 0.4 Gy for 15 MV X-rays[11]. For doses above D_1 , the cell's repair mechanism is enhanced. At this stage, ATM transmits signals to p53, increasing the repair rate above the damage rate, which leads to IRR, reflecting a radioprotective effect[35, 36]. For p53 wild-type cells, repair rates are rapid, resulting in a steeply rising survival curve. In contrast, for p53 mutant cells, the normal distribution curve is broader, and σ is larger.

When the dose reaches D_2 , the damage rate also increases with the dose but remains lower than the repair rate up to D_2 . Beyond D_2 , as the dose increasing, the ATM activation levels stabilize, while the damage rate significantly exceeds the repair rate, consistent with the LQ model.

In conclusion, this paper describes the HRS/IRR phenomenon from the perspective of biomolecular, exploring related damage and repair mechanisms that merit further investigation.. For instance, this phenomenon can also be interpreted from an perspective of immunity. Beyond D_1 inflection point, immunity gradually increases, reducing cell damage. Numerous studies have reported the effects of low-dose radiation on immune function[37].Low-dose radiation is known to up-regulate immune factor TCR/CD3, and it suggested that the ability of lymphocyte to receive antigen stimulation was increased. Additionally, CD2 expression in T lymphocytes is significantly up-regulated after low dose radiation exposure[38].

Declarations

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Competing Interests The authors declare that they have no conflict of interest.

Author Contributions Zhao Xu, Taosheng Li, and Qi Liu contributed to the conception and design of this review. Zhao Xu and Guangyan Feng wrote the original draft and created all the figures and tables. Wenyi Li, Yu Lu and Ziyi Ding critically revised and edited the review. All authors read and approved the final version of the manuscript.

Data Availability No data were generated or analysed during this study.

Ethics Declaration Not applicable.

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